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non-specific symptoms rather than the physical signs of life-threatening illness that are traditionally taught in medical schools. Recognition of these non-specific symptoms by doctors depends more on obtaining a careful history from the parents than on physical examination. Few parents, too, seem to have appreciated the importance of unusual drowsiness, irritability, excessive crying, an altered character to the cry, or being off feeds, either in isolation or as markers of deterioration in children with respiratory or gastrointestinal illnesses.

We are not suggesting that all the children who had major symptoms should have been referred to hospital or that they would have benefited from the earlier prescription of drugs. Indeed, as drug treatment is rarely indicated for respiratory illnesses and gastroenteritis at this age, it might be counter-productive, giving false reassurance to parents so that they might delay recalling the doctor despite the child's evident deterioration. It seems essential, however, that any child with non-specific symptoms—which may be the only evidence of developing meningitis or septicaemia—should be kept under close review. If home circumstances are satisfactory, if the parents can be relied on to call for further help at the first sign of deterioration (such signs having been clearly explained to them), and if the primary care team can undertake close supervision then continued observation of the child at home will often be appropriate. We are still investigating how far these conditions are not being fulfilled and which are the crucial deficiencies in the use and provision of health services for acutely ill young children. A definition of which children would be safer under observation in hospital is needed but not yet clear. Closer analysis of the data and comparisons between the histories given by the parents, family doctor, and health visitor may establish that non-specific symptoms should determine when hospital referral becomes appropriate, especially if there is already evidence of respiratory illness or gastroenteritis.

The construction and use of a clinical classification of deaths occurring unexpectedly at home is only one step towards understanding a complex medical and social problem that almost

certainly needs several different solutions. A later stage of the study will be to try to match the histories with the histology, so that we can interpret more precisely the importance of minor pathological changes, especially when the fatal process may have proceeded too rapidly for major tissue changes to have developed. Comparing pathological findings with the symptoms elicited may also help to indicate cases in which the observation or history was inadequate.

Once those children dying of inadequately recognised illness have been identified it should be possible to define the epidemiological characteristics of children who die unexpectedly despite appearing to be well. This is a crucial step before prospective investigations of cardiac, respiratory, neurological, and other physiological mechanisms of death can be undertaken in manageable numbers of children.

Such fundamental research is a long-term commitment. The preliminary results of this study show that a large proportion of deaths might be prevented now if existing knowledge were better applied. There is an urgent need to improve the recognition by both doctors and parents of non-specific symptoms as markers of severe illness in young children and their understanding of the necessity for rapid and appropriate action.

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Severe hyponatraemia in hospital inpatients

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Summary and conclusions

A prospective study of severe hyponatraemia in adult hospital inpatients showed that 44 patients had plasma sodium concentrations below 125 mmol(mEq)/l. Eighteen cases (41%) were iatrogenic, caused by diuretic treatment or postoperative administration of intravenous 5% dextrose, or both. Chest infection, a seldom-recognised and ill-understood cause of hyponatraemia, proved more common than carcinoma of the bronchus. Thirty-one patients had symptoms attributable to the

hyponatraemia, but these were severe in only five cases. Analysis of blood and urine was of no value in distinguishing the different diagnostic groups in an emergency.

Introduction

Many studies of cases of hyponatraemia have been reported, some of which have been concerned with the so-called syndrome of inappropriate antidiuretic hormone secretion.¹⁻⁴ We report here an investigation into the incidence of severe hyponatraemia in an adult hospital population, the relative frequency of different causes, and the clinical importance of the condition. We have also assessed the clinical value of analyses of urine and blood in distinguishing the causes.

Methods

We were informed by the laboratory of all patients aged over 14 years with a plasma sodium concentration of under 125 mmol(mEq)/l. Patients were assessed clinically by one of us (PK or DM), with particular reference to the state of hydration, possible symptoms attributable to hyponatraemia, and the probable cause of the condition.

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Simultaneous blood and urine samples were collected, and only patients with a plasma sodium concentration below 125 mmol/l in this specimen were considered further.

Plasma sodium, potassium, and urea and urinary urea concentrations were measured with a Technicon AA₂ autoanalyser; plasma and urinary osmolalities by freezing-point depression with an Advanced osmometer; plasma and urinary creatinine concentrations with a Technicon AA₁ autoanalyser; plasma and urinary magnesium and calcium concentrations by an atomic absorption spectrophotometer; and urinary sodium and potassium concentrations by a flame photometer.

Results

We observed 44 patients (17 men, 27 women) with a plasma sodium concentration below 125 mmol/l over 10 months. This represented 0.9% and 0.4% respectively of the total medical and surgical admissions during the period. The patients were aged 23-90 (median 72) years, and the plasma sodium concentrations ranged from 110 to 124 (median 119) mmol/l.

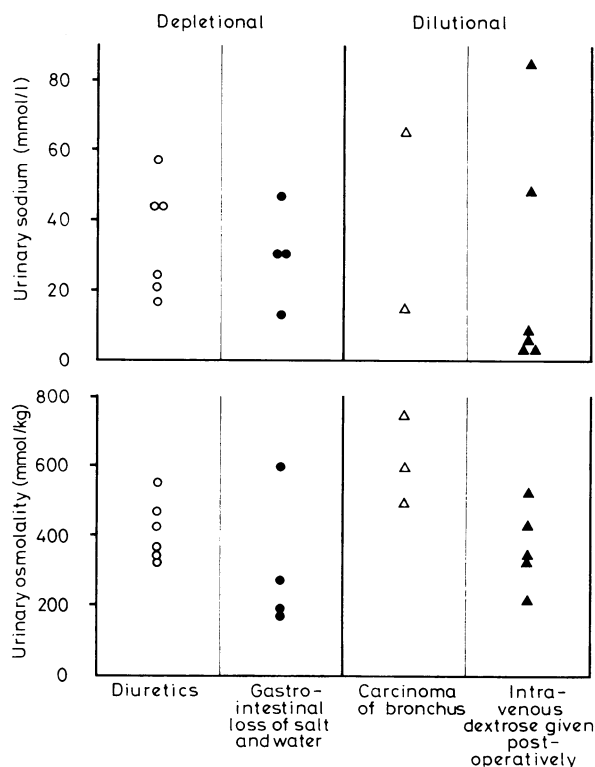
In eight patients the hyponatraemia was attributed solely to diuretics, used as maintenance treatment after previous heart failure. None of these patients had peripheral or pulmonary oedema when hyponatraemic, and only three were clinically dehydrated. Ten patients had received intravenous 5% dextrose after surgery; five of these were also receiving maintenance diuretic treatment. Nine cases were attributed to gastrointestinal and one to renal loss of salt and water. Eleven cases were associated with chest disease—seven with chest infections and four with carcinoma of the bronchus. One patient had liver failure, and in four severely ill patients there was no recognised cause of hyponatraemia.

Symptoms attributable to hyponatraemia, such as mental confusion, lassitude, anorexia, nausea, and headache,³ are nonspecific, and it is difficult in practice to judge whether hyponatraemia or the underlying condition is responsible. Nevertheless, the hyponatraemia was considered to be the cause of symptoms in 31 patients (70%). In five cases (three iatrogenic) the symptoms were severe: three patients were grossly confused, one was comatose, and one had fits. In two of these cases and one other hyponatraemia had led to the patient's admission. The hyponatraemia and relevant symptoms cleared rapidly after diuretics or intravenous dextrose infusion had been stopped, chest infections treated, or salt and water losses replaced. Water restriction or hypertonic saline was not needed, and although 12 deaths occurred among the 44 patients hyponatraemia did not play a part in any.

Results of biochemical investigations were not received in many cases owing to administrative problems. But there was no apparent selection, and we do not believe that this invalidates our conclusions. The investigations proved unhelpful in differentiating the causes of hyponatraemia. The figure shows that urinary sodium concentrations and osmolality values overlapped considerably between groups divided arbitrarily according to whether the hyponatraemia had a "dilutional" or "depletional" cause. Similar comparisons using plasma:urine ratios and combinations of creatinine, sodium, potassium, magnesium, and calcium concentrations and osmolality showed a similar scatter. Only one of the patients with diuretic-induced hyponatraemia had a plasma potassium concentration under 3.0 mmol/l.

Discussion

Although all patients with a plasma sodium concentration below 125 mmol/l probably have symptoms,⁶ hyponatraemia is rarely diagnosed on clinical grounds, and most of the initial blood tests in our series were routine. The true prevalence of severe hyponatraemia in an adult inpatient population may well be much greater than our data suggest. Two-fifths of our cases were iatrogenic. At least half of the cases studied by Arieff *et al*⁶ were iatrogenic, though their group of patients was more selected than ours. Theoretically hyponatraemia should be less of a problem with "loop" diuretics than with thiazides.⁷ Of our cases, five were associated with frusemide treatment and eight with thiazides; some patients in both groups were also receiving potassium-retaining diuretics. The absence of clinical dehydration in most of the patients with diuretic-induced hyponatraemia confirms views that sodium depletion plays a relatively minor part in this condition.⁴



Urine sodium concentrations and osmolality in patients with severe hyponatraemia divided arbitrarily according to whether the hyponatraemia had a depletional or dilutional cause.

Conversion: SI to traditional units—Sodium: 1 mmol/l = 1 mEq/l. Osmolality: 1 mmol/kg = 1 mosmol/kg.

There are many stimuli for release of antidiuretic hormone after surgery.⁸ The combination of postoperative water load with 5% dextrose and reduced ability to excrete free water owing to diuretic treatment appears to be a particularly potent cause of severe postoperative hyponatraemia.

Like Thomas *et al*,³ we found that bacterial chest infections frequently cause severe hyponatraemia. Biochemical analysis of blood and urine showed no characteristic values in these patients consistent with the data of Thomas *et al*³; their data also show a wide range of urine sodium and osmolality values within other diagnostic groups. Reduced water excretion in sodium-depleted states,⁹ continuing sodium excretion with overhydration,¹ and variations in salt and water intakes are among factors that lead to such variability within, and overlap between, diagnostic groups. Divalent ion excretion as a marker of plasma volume expansion¹⁰ does not appear to be of diagnostic value. Classical clinical and biochemical criteria for the syndrome of inappropriate secretion of antidiuretic hormone were satisfied in cases with different aetiologies; this reinforces doubts about the clinical usefulness of this concept in the absence of ectopic production of antidiuretic hormone.³

This investigation did not include patients with hyponatraemia due to severe heart failure, acute renal failure, or endocrine deficiency and may to some extent reflect local clinical practice. We believe, however, that many cases of hyponatraemia in hospitals are avoidable. Inappropriate treatment appears to be more important than inappropriate secretion of antidiuretic hormone. Particular care must be taken with intravenous fluid regimens in patients undergoing surgery while taking diuretics. Biochemical analysis of urine appears to play little or no part in elucidating the cause or in the management of severe hyponatraemia in an emergency. Measurements of blood concentrations of antidiuretic hormone are also unlikely to be of help.³

Although hyponatraemia only occasionally gives rise to severe symptoms in its own right, it may be a more important cause of

morbidity than hypokalaemia in patients on long-term diuretic treatment.

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Evidence for a primary autoimmune type of diabetes mellitus

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Summary and conclusions

Sixty-eight patients with longstanding diabetes and persistent islet-cell antibody and 35 with coexistent diabetes and Graves's disease or primary myxoedema were studied with particular reference to the HLA system and autoantibody patterns. A higher incidence of HLA-B8 than normal was observed in the two groups. An additive relative risk exists when type I diabetes and autoimmune thyroid disease coexist, indicating that different HLA-linked genes may confer susceptibility to the pancreatic and thyroid disorders. Other characteristics, including female predominance, a later onset of diabetes, and a strong family history of autoimmune endocrinopathy, provide further evidence that this form of diabetes is aetiologically distinct from that generally seen in children.

These results support the hypothesis of a primary autoimmune type of diabetes mellitus.

Introduction

Much interest has been focused on the biological importance of the underlying genetic determination and associated autoimmune phenomena in insulin-dependent diabetes irrespective of the age of onset (type I diabetes^{1,2}). There is a significant positive association between HLA-B8 and several organ-specific autoimmune disorders including Graves's disease, Addison's disease, and myasthenia gravis.³ HLA-B8 is also associated with type I diabetes, but there is interesting evidence of a more complex relation in this disease, with a double axis of HLA

determinants conferring susceptibility and a single axis conferring protection.^{1,4} In people positive for HLA-B8 the relative risk of developing either diabetes or Graves's disease is increased two to three times.^{1,3} No studies of primary myxoedema have been reported, and the association between Hashimoto's disease and the HLA system is still controversial.^{5,6}

The increased prevalence of thyrogastric antibodies in patients with insulin-dependent diabetes is well recognised.⁷ Islet-cell antibodies (ICA) are prominent and persistent in patients with polyendocrine disease and are found more transiently in children with uncomplicated diabetes.^{8,9} Accordingly it has been suggested that pancreatic antibodies might be used as a marker for subdividing type I diabetes into two syndromes of different aetiology—namely, "juvenile" diabetes (type Ia), in which the autoimmune marker may occur in response to hypothetical viruses, and "primary autoimmune" or "polyendocrine" diabetes (type Ib).¹⁰ Results of a recent study in children has supported this dual hypothesis, since ICA persisting for more than three years were strongly associated with the presence of other organ-specific antibodies in the patients and their families.¹¹

An important question is whether the same or separate genes in linkage disequilibrium with HLA-B8 confer susceptibility to diseases in different endocrine organs. In order to elucidate this further we studied longstanding diabetics, some of whom had coexistent primary thyroid disease.

Patients and methods

We studied two groups of patients as follows:

Group 1—This group comprised 68 longstanding diabetics (mean duration of diabetes 19.5 years) with persistent ICA, whom we investigated with particular reference to clinical characteristics and other immunological features. Sixty-one patients were insulin dependent, and seven had been receiving diet and treatment by mouth for a considerable time (14-39 years). Thirty-nine of the insulin-dependent group who had no clinical or biochemical evidence of other autoimmune endocrinopathy were HLA-typed.

Group 2—This group comprised 35 patients with coexistent type I diabetes and thyroid disease. All were receiving insulin. Eighteen patients had presented with classical features of Graves's disease. The diagnosis of primary myxoedema in 17 patients was made on clinical and metabolic features; none of these patients had previously been thyrotoxic or had a palpable goitre suggestive of Hashimoto's disease.

Methods—We carried out HLA-A and B typing for 34 specificities using a standard microlymphocytotoxicity method.¹² Relative risks were computed by the Woolf method¹³ as modified by Haldane.¹⁴

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